UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,789	01/28/2005	Hajime Hiramatsu	09724.0001	9489

22852 7590 03/27/2007

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
NASHED, NASHAAT T	
ART UNIT	PAPER NUMBER
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,789	HIRAMATSU ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *7-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☒ Claim(s) *4-6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/19/05 & 7/22/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's election without traverse of Group I, claims 1-6, in the reply filed on February 28, 2007 is acknowledged.

Claims 1-6 are under consideration in this Office action.

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Figure 2 does not show the diffraction pattern as indicated in the Figure description to Figure 2. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s). In particular, 37 CFR 1.821, which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Thus, each time the phrases human dipeptidyl peptidase IV or shDPPIV appear in the specification, Figure Description and/or the claims, a sequence identification number should be accompanied each one at each occurrence. Applicant should note that he atomic coordinates of Table 4 represents the disclosure of a linear amino acid sequence of more than four amino acid, and therefore an amino acid sequence identification number should appear at the heading of the Table or in the figure description.

The use of the trademarks such as "TAQ DYEDEOXY TERMINATOR CYCLE SEQUENCE KIT" at page 50, lines 9-10, "VIVAFLOW 50", "AMICON", "HITRAP", and "RESOURCE Q" at page 53, lines 7, 8, 11, and 21, respectively, and "CENTRICON" and "CRYSCHEM" at page 54, lines 4 and 11, respectively, have been noted in this application. They should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claims 4-6 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claims 4-6 cannot depend from a multiple dependent

claim. See MPEP § 608.01(n). Accordingly, the claims 4-6 have not been further treated on the merits.

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3 are directed to all possible crystals of dipeptidyl peptidase IV (DPPIV) from any biological source, a fragment thereof, or any fusion protein thereof, wherein the crystal capable of diffracting X-ray. The specification, however, only provides single representative species of these crystals containing only the glycosylated amino acid sequence of residues 33-766 of SEQ ID NO: 2 at five positions fused to a His-Tag protein with unknown sequence in the orthorhombic space group $2_12_12_1$ and unit cell dimension of a = 118.0, b = 125.9, and c = 136.8 with $\alpha=\beta=\gamma=$ 90 degrees. See page 55, lines 12-15. There is no disclosure of any particular relationship between the amino acid sequence of the DPPIV and the crystallization conditions.

The court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] name chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." UC California v. Eli Lilly (43 USPQ2d 1398). For claims drawn to genus, MPEP section 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Also, MPEP section 2163 states that a representative number of species mean that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. At the time of invention, the full-length DPP-IV was well known in the art along with variants from other mammals as well as its biological role in regulating several biological processes. The instant application describes the crystallization of a modified

fragment of human DPP-IV, presumably, consisting of undefined His-Tag fused to one of the termini of residues 33-766 of the amino acid sequence of SEQ ID NO: 2 (see paragraph 65) under the specific condition described at page 54. In general, for a species of crystal to be adequately and structurally described, the following must be adequately described: (i) the exact chemical composition of the crystal, i.e., the structure feature of all molecules in the crystal including the amino acid sequence of any protein or nucleic acid, (ii) the space group of the crystal; and (iii) the unit cell dimension of the crystal. Neither the applicants nor the prior art has described a crystal or the crystallization of the native DPP-IV. Thus, the specification fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the space group in claim 4. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all-possible crystals comprising any DPP-IV having any amino acid sequence, fragments and mutants thereof as well as any fusion protein thereof. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses all-possible orthorhombic crystals any DPP-IV having any amino acid sequence, fragments and mutants thereof as well as any fusion protein thereof. The specification provides guidance and examples in the form of an assay to obtain a protein consisting of residues 33-766 of the amino acid sequence of SEQ ID NO: 2 glycosylated at 5 positions fused to a His-Tag, presumably at the C-terminal under the specific crystallization conditions described at page 54 of the specification. While molecular biological techniques and genetic manipulation to make any protein, a general crystallization methods for proteins, and synthetic method to make any compound that binds to any DPP-IV are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of a particular protein and its complexes is lacking. It is well established in the art that obtaining a protein and its complexes in a

crystal form is highly unpredictable without any clear expectation of success, and any change in a given crystallization condition including any minor alteration could alter the crystal form and its diffraction characteristics or even lack of crystal formation. It is now evident that protein crystallization is the major hurdle in protein structure determination. For this reason, protein crystallization has become a research subject in and of itself, and is not simply an extension of structure biologist or crystallographer's laboratory. There are many references that describe the difficulties associated with protein crystals. See for example, Gilliland *et* al, (*Curr. Open in Struct. Biol.* 1996, 6, 595-603) in particular page 600, left column second paragraph; Ke *et al.* (Methods, 2004, 34, 408-414); and Wiencek, J. M. (Ann. Rev. Biomed. Eng. 1999, 1, 505-534). Thus, the skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein which may crystallize under specific crystallization condition, it mutants may or may not crystallize under the same condition. In many cases, a protein that can't be crystallized, one of its specific mutants might be crystallized. Even if a crystal is obtained, it may or may not be suitable for protein structure determination by X-ray. Thus, searching for a crystallization conditions for a protein and its complexes that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify a crystal for a protein having DPP IV activity, or any insertion, deletion or addition mutants thereof suitable for structure determination X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of crystallization conditions or mutants of any mammalian DPP-IV, which can be crystallized where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the exact amino acid sequences of DPP-IV and identify a crystallization conditions that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. They are narrative in nature and appear to be a literal translation from a foreign language. The following are the reasons for the rejection:

(a) The phrase "having characteristics sufficient to ensure a resolution capable of analyzing its three-dimensional structure up to ....." in claim 1 renders the claim indefinite because the resulting claim does not set forth

the metes and bound of the patent protection desired. In rephrasing the claim, applicants should be reminded that the structure determined by the X-ray diffraction method is that of the protein in the crystal and not the crystal. The crystal is defined by the chemical composition of the crystal including the amino acid sequence, the space group and the unit cell dimension. Also, the examiner does not know any other characteristics in a crystal needed for obtaining a protein structure other than a diffraction of X-ray radiation at high resolution.

(b) Claim 2 is considered indefinite because it fails to comply with the sequence rule. Human dipeptidyl peptidase IV is disclosed in the specification and the sequence listing as SEQ ID NO: 2 and replace "a" before "full-length with "the". Applicants must insert the sequence identification number to overcome this rejection.

(c) The phrase "comprising a region located at the extramembrane in a full" renders the claim indefinite because the resulting claim does not set forth the desired patent protection desired. For examination purposes only, it is assumed that the applicants mean residues 33-766 of SEQ ID NO: 2.

(d) The phrase "transmembrane region" in claim 3 renders the claim indefinite because the resulting claim does not set forth the desired patent protection desired. The exact boundary of the region is not defined by the specification and one of ordinary skill in the art would not know what the applicants mean. For examination purposes only, it is assumed residues 1-32 of SEQ ID NO: 2.

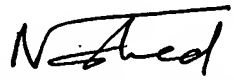
(e) The phrase "Tag peptide" in claim 3 renders the claim indefinite because the resulting claim does not set forth the desired patent protection desired. It is noted that the Tag is exemplified by the specification as a His-Tag, but no specific Tag-peptide is indicated.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen K. Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656